CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for: **074591**

Trade Name : GLYBURIDE TABLETS USP (MICRONIZED)

Generic Name: Glyuburide Tablets USP (Micronized) 1.5mg, 3mg, 4.5mg and 6mg

Sponsor : Mova Pharmaceutical Corporation

Approval Date: December 22 , 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074591

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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074591

APPROVAL LETTERS

ANDA 74-591

FEB 11 1997

MOVA Pharmaceutical Corporation
Attention: Claribel Velez
Calle A (Zafiro) Carr. 1 Km. 34.18 Urb. Industrial
Villa Blaca, Caguas, PR 00725

Dear Madam:

Reference is made to your abbreviated new drug application dated December 9, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Glyburide Tablets (micronized), 1.5 mg, 3 mg, 4.5 mg, and 6 mg.

Reference is also made to your amendments dated October 10, October 29, November 7, 1996 and January 31, 1997.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved.** This determination is based upon information available to the Agency at this time, which includes information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug products. Therefore, this determination is subject to change on the basis of new information that may come to our attention. This letter does not address notice issues related to the 180-day exclusivity provisions under section 505(j)(4)(B)(iv) of the Act.

The listed drug product referenced in your application is subject to a period of patent protection which expires on April 5, 2002, (patent 4,735,805) and April 10, 2007, (patent 4,916,163). However, you have informed us that litigation is underway in the United States District Court for the District of Puerto Rico, involving a challenge to the patent (Upjohn Company, a Michigan Corporation, v. MOVA Pharmaceutical Corporation, a Corporation of the Commonwealth of Puerto Rico, Civil Action No. 95-1378PG.) Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in section 505(j)(4)(B)(iii) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or,

b. the date of court decision [505(j)(4)(B)(iii) (I), (II), or (III)], which has been interpreted by the Agency to mean the date of the final order or judgement of that court from which no appeal can be or has been taken, or,

c. the patent has expired, and

2. The Agency is assured there is no new information that would affect whether final approval should be granted.

Because the Agency is granting a tentative approval for this application, when you believe that your application may be considered for final approval, you must amend your application to notify the Agency whether circumstances have or have not arisen that may affect the effective date of final approval. Your amendment must provide:

1. a copy of a final order or judgement from which no appeal may be taken (which might not be the one from the district court), or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

b. a statement that no such changes have been made to the application since the date of tentative approval.

Any changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made.

In addition to, or instead of, the amendments referred to above, the Agency may, at any time prior to the final date of approval, request that you submit amendments containing the information requested above.

Failure to submit either or both amendments may result in rescission of this tentative approval determination, or delay in issuance of the final approval letter.

The drug product that is the subject of this abbreviated application may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under Section 501 of the Act. Also, until the Agency issues the final approval letter, these drug products will not be listed in the Agency's "Approved Drug Products with Therapeutic Equivalence Evaluations" list.

The amendment should be designated as a MINOR AMENDMENT in your cover letter. Before you submit the amendment, please contact Sheila M. O'Keefe, Project Manager, at (301) 594-0370, for further instructions.

Sincerely yours

-2/11/97

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 74-591

DEC 22 1997

Mova Pharmaceutical Corporation
Attention: Angel L. Rodriguez-Arce
P.O. Box 8639
Caguas, PR 00726

Dear Sir:

This is in reference to your abbreviated new drug application dated December 9, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Glyburide Tablets USP (Micronized), 1.5 mg, 3 mg, 4.5 mg and 6 mg.

Reference is also made to your amendments dated August 26, October 24, October 31, November 6, and December 10, 1997.

The listed drug product referenced in your application is subject to periods of patent protection which expire on April 5, 2005 (patent 4,735,805) and April 10, 2007 (patent 4,916,163). Your application contains a patent certification under Section 505(j)(2)(A)(vii)(IV) of the Act stating that your manufacture, use, or sale of Glyburide Tablets, USP (Micronized) will not infringe the patents or that the patents are otherwise invalid. You have informed the Agency that The Upjohn Company initiated a patent infringement suit regarding patent 4,916,163 against you in the United States District Court for the District of Puerto Rico (The Upjohn Company v. Mova Pharmaceutical Corporation, Civil Action No. 95-1378PG), and that on December 2, 1997, the District Court ruled that judgement pursuant to a jury verdict be entered on behalf of Mova.

You have also informed the Agency that the 30-month period identified in Section 505(j)(4)(B)(iii) of the Act, during which time FDA was precluded from approving your application, has expired, and that the court did not extend the period.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Glyburide Tablets USP, (Micronized) 1.5 mg, 3 mg, 4.5 mg and 6 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Glynase PresTab Tablets, 1.5 mg, 3 mg, 4.5 mg, and 6 mg, respectively, of The Pharmacia and Upjohn Company). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

12/19/97

Roger L. Williams, M.D.
Deputy Center Director for
Pharmaceutical Science
Center for Drug Evaluation and Research

MOVA PHARMACEUTICAL CORPORATION
P.O. Box 8639
Caguas, Puerto Rico 00726
(787) 746-8500

October 31, 1997

Mr. Douglas Sporn
Director, Office of Generic Drugs
CDER, FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 74-591 GLYBURIDE TABLETS (micronized)
6.0mg, 4.5mg, 3.0mg, 1.5mg

MINOR AMENDMENT AND
NOTIFICATION OF 30 MONTH EXPIRATION

Dear Mr. Sporn:

This correspondence is according to the instructions received in your Tentative Approval Letter dated February 11th, 1997 for the above referenced ANDA.

In that letter you requested that we notify the agency of circumstances that have arisen that may affect the effective date of final approval. This amendment provides:

1. Relevant information: The status of the 30 month period provided for in section 505(j)(4) (B)(iii) from the date of receipt by Upjohn of the 45 day notice is as follows: The time has expired and has not been extended by the court. We have attached for your reference a copy of the notification to the Upjohn Company and receipt confirmation, which we originally submitted to your office on February 17th, 1995. Attachment I.

2. Updated Information related to labelling and the CMC section of this application.

Since the receipt of the tentative approval letter of February 11, 1997 several minor changes have occurred that do not affect the conditions outlined in the abbreviated application. These are:

a) Changes to raw material Quality Standards and/or Test Methods to reflect the current USP and Supplement requirements.

b) Changes to Finished Product Quality Standards and Test Methods to reflect the current USP and Supplement requirements.

c) Manufacturing instructions of the commercial batch sizes were revised to include:

c) The addition of a packaging configuration of 500 tablets per bottle, which is within the already established range of 100-1000 count utilizing the same container/closure system as the 1000 count bottle.

d) Labelling updates to reflect this additional 500 count configuration (which was submitted as a Minor Amendment to the application on October 24th, 1997).

If you have any further question please contact me at (787) 746-8500, extension 108.

Claribel Vélez

Claribel Vélez
Director, Regulatory Affairs and Compliance

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074591

FINAL PRINTED LABELING

Usual Dosage: See package circular for full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

Keep tightly closed.

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by
MOVA PHARMACEUTICAL CORPORATION
Caguas, Puerto Rico 00725, USA

MOVA

GLYBURIDE TABLETS (micronized)

1.5 mg

NDC 55370-146-09

1000 TABLETS

CAUTION: Federal law prohibits dispensing without prescription.

LOT #:

EXP. DATE:

DEC 2 1997

6225700MV

3 55370-146-09 5

ISSUED 7/95

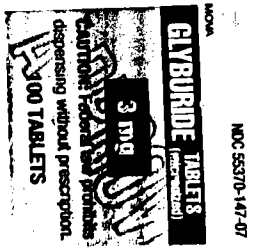
Usual Dosage: See package circular for full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

Keep tightly closed.

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by
MOVA PHARMACEUTICAL CORPORATION
Caguas, Puerto Rico 00725, USA



NDC 55370-147-07

LOT #:

EXP. DATE:

DEC 2 1997

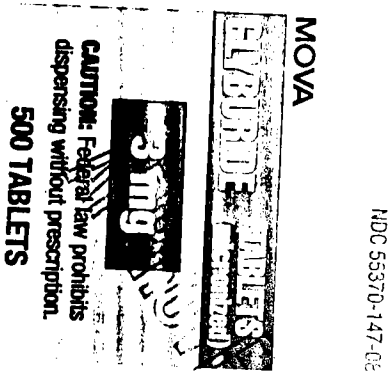
3 55370-147-07 8

6225800MV

ISSUED 7/95

Usual Dosage: See package circular for full prescribing information.
Dispense in a tight, light-resistant container with a child-resistant closure.
Keep tightly closed.
Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
MOVA PHARMACEUTICAL CORPORATION
Caguas, Puerto Rico 00725, USA



NDC 55370-147-08

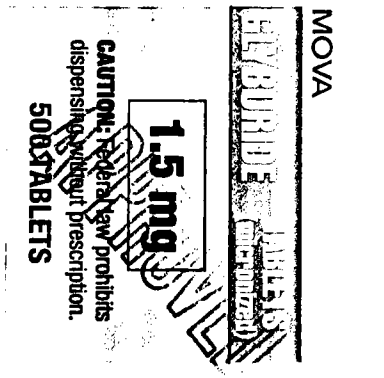
LOT #:

EXP. DATE:

6246700MV ISSUED 6/97

Usual Dosage: See package circular for full prescribing information.
Dispense in a tight, light-resistant container with a child-resistant closure.
Keep tightly closed.
Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
MOVA PHARMACEUTICAL CORPORATION
Caguas, Puerto Rico 00725, USA



NDC 55370-146-08

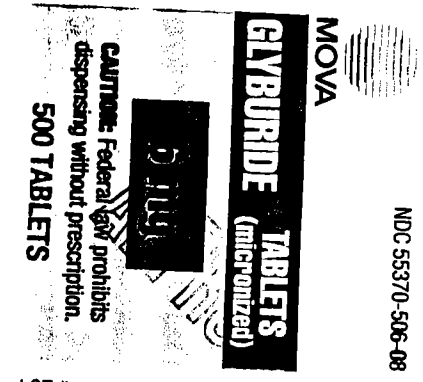
LOT #:

EXP. DATE:

6246600MV ISSUED 6/97

Usual Dosage: See package circular for full prescribing information.
Dispense in a tight, light-resistant container with a child-resistant closure.
Keep tightly closed.
Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by:
MOVA PHARMACEUTICAL CORPORATION
Caguas, Puerto Rico 00725, USA



NDC 55370-506-08

LOT #:

EXP. DATE:

6246500MV ISSUED 6/97

Usual Dosage: See package circular for full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

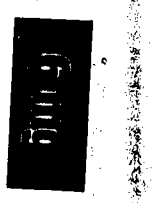
Keep tightly closed.

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by
MOVA PHARMACEUTICAL CORPORATION
Caguas, Puerto Rico 00725, USA

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS



GLYBURIDE TABLETS (micronized)

MOVA

NDC 55370-506-09

LOT #:

EXP. DATE:

6226300MV

ISSUED 7/95

Usual Dosage: See package circular for full prescribing information.
Dispense in a tight, light-resistant container with a child-resistant closure.
Keep tightly closed.
Store at controlled room temperature 15°-30°C (59°-86°F).
Manufactured by
MOVA PHARMACEUTICAL CORPORATION
Caguas, Puerto Rico 00725, USA

CAUTION: Federal law prohibits dispensing without prescription.
100 TABLETS

MOVA GLYBURIDE TABLETS (micronized)

NDC 55370-146-07

LOT #:
EXP. DATE:
DEC 22 1997

3 55370-146-07 1

6225600MV ISSUED 7/95

Usual Dosage: See package circular for full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

Keep tightly closed.

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by
MOVA PHARMACEUTICAL CORPORATION
Caguas, Puerto Rico 00725, USA

MOVA

GLYBURIDE TABLETS (micronized)

4.5 mg

NDC 55370-149-09

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

LOT #:

EXP. DATE:

1997

6226100MV

3 55370-149-09 6

ISSUED 7/95

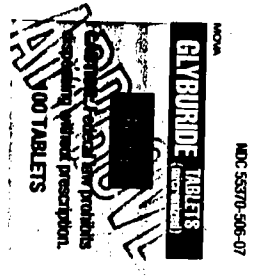
Usual Dosage: See package circular for full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

Keep tightly closed.

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by
MOVA PHARMACEUTICAL CORPORATION
Caguas, Puerto Rico 00725, USA



LOT #:

EXP DATE:

DEC 2 1997

3 55370-506-07 3

6226200MV

ISSUED 7/95

Usual Dosage: See package circular for full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

Keep tightly closed.

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by
MOVA PHARMACEUTICAL CORPORATION
Caguas, Puerto Rico 00725, USA

MOVA

GLYBURIDE TABLETS (micronized)

3 mg

CAUTION: Federal law prohibits dispensing without prescription.

1000 TABLETS

NDC 55370-147-09

LOT #:

EXP. DATE:

DEC 2 1997

6225900MV

3 55370-147-09 2

ISSUED 7/95

Usual Dosage: See package circular for full prescribing information.

Dispense in a tight, light-resistant container with a child-resistant closure.

Keep tightly closed.

Store at controlled room temperature 15°-30°C (59°-86°F).

Manufactured by
MOVA PHARMACEUTICAL CORPORATION
Caguas, Puerto Rico 00725, USA

MOVA

GLYBURIDE TABLETS (micronized)

4.5 mg

CAUTION: Federal law prohibits dispensing without prescription.

100 TABLETS

NDC 55370-149-07

LOT #:

EXP. DATE:

DEC 2 1997

3 55370-149-07 2

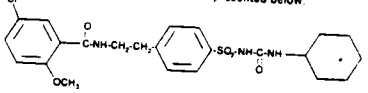
6226000MV

ISSUED 7/95

GL[illegible]IRIDE TABLETS (micronized)

DESCRIPTION

Glyburide tablets (micronized) contain micronized (smaller particle size) glyburide, which is an oral blood-glucose-lowering drug of the sulfonylurea class. Glyburide is a white, crystalline compound. Each tablet, for oral administration, contains 1.5 mg, 3 mg, 4.5 mg, or 6 mg of micronized glyburide. Inactive ingredients: Colloidal Silicon Dioxide, Pregelatinized Starch, Lactose Monohydrate, Magnesium Stearate. In addition, the 3 mg strength contains FD&C Blue No. 1, the 4.5 mg contains FD&C Blue No. 1, D&C Yellow No. 10, FD&C Yellow No. 6; and the 6 mg tablet contains D&C Yellow No. 10. The chemical name for glyburide is 1-[[p-[2-(5-chloro-o-anisamido) ethyl]phenyl]-sulfonyl]-3-cyclohexylurea and the molecular weight is 494.01. The structural formula is represented below:



CLINICAL PHARMACOLOGY

Actions

Glyburide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. The mechanism by which glyburide lowers blood glucose during long-term administration has not been clearly established. With chronic administration in Type II diabetic patients, the blood glucose lowering effect persists despite a gradual decline in the insulin secretory response to the drug. Extrapancreatic effects may be involved in the mechanism of action of oral sulfonylurea hypoglycemic drugs.

The combination of glyburide and metformin may have a synergistic effect, since both agents act to improve glucose tolerance by different but complementary mechanisms.

Some patients who are initially responsive to oral hypoglycemic drugs, including glyburide, may become unresponsive or poorly responsive over time. Alternatively, glyburide may be effective in some patients who have become unresponsive to one or more other sulfonylurea drugs.

In addition to its blood glucose lowering actions, glyburide produces a mild diuresis by enhancement of renal free water clearance. Disulfiram-like reactions have very rarely been reported in patients treated with glyburide.

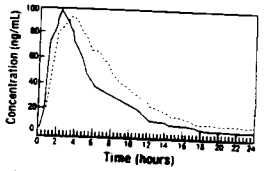
Pharmacokinetics

Single dose studies with glyburide tablets (micronized) in normal subjects demonstrate significant absorption of glyburide within one hour, peak drug levels at about two to three hours, and low but detectable levels at twenty-four hours.

Bioavailability studies have demonstrated that micronized glyburide tablets 3 mg provide serum glyburide concentrations that are not bioequivalent to those from nonmicronized glyburide tablets 5 mg. Therefore, the patient should be retitrated.

It has been reported that in a single-dose bioavailability study (see Figure A) in which subjects received micronized glyburide tablets 3 mg and nonmicronized glyburide tablets 5 mg with breakfast, the peak of the mean serum glyburide concentration-time curve was 97.2 ng/mL for the micronized glyburide tablets 3 mg and 87.5 ng/mL for nonmicronized glyburide tablets 5 mg. The mean of the individual maximum serum concentration values of glyburide (Cmax) from micronized glyburide tablets 3 mg was 106 ng/mL and that from nonmicronized glyburide tablets 5 mg was 104 ng/mL. The mean glyburide area under the serum concentration-time curve (AUC) for this study was 568 ng x hr/mL for micronized glyburide tablets 3 mg and 746 ng x hr/mL for nonmicronized glyburide tablets 5 mg.

Figure A



——— Glyburide tablets (micronized)
- - - - - Glyburide tablets (nonmicronized)

Mean serum levels of glyburide, as reflected by areas under the serum concentration-time curve, increase in proportion to corresponding increases in dose. Multiple dose studies with glyburide in diabetic patients demonstrate drug level concentration-time curves similar to single dose studies, indicating no buildup of drug in tissue depots.

In a steady-state study in diabetic patients receiving micronized glyburide tablets 6 mg once daily or micronized glyburide tablets 3 mg twice daily, no difference was seen between the two dosage regimens in average 24 hour glyburide concentrations following two weeks of dosing. The once-daily and twice-daily regimens provided equivalent glucose control as measured by fasting plasma glucose levels, 4 hour postprandial glucose AUC values, and 24 hour glucose AUC values. Insulin AUC response over the 24 hour period was not different for the two regimens. There were differences in insulin response between the regimens for the breakfast and supper 4 hour postprandial periods, but these did not translate into differences in glucose control.

The serum concentration of glyburide in normal subjects decreased with a half-life of about four hours.

In single dose studies in fasting normal subjects who were administered glyburide tablets (micronized) in doses ranging from 1.25 mg to 5 mg, the degree and duration of blood glucose lowering is

different but complementary mechanisms.

Some patients who are initially responsive to oral hypoglycemic drugs, including glyburide, may become unresponsive or poorly responsive over time. Alternatively, glyburide may be effective in some patients who have become unresponsive to one or more other sulfonylurea drugs.

In addition to its blood glucose lowering actions, glyburide produces a mild diuresis by enhancement of renal free water clearance.

Disulfiram-like reactions have very rarely been reported in patients treated with glyburide.

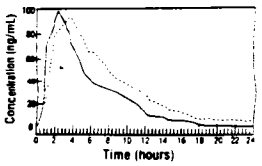
Pharmacokinetics

Single dose studies with glyburide tablets (micronized) in normal subjects demonstrate significant absorption of glyburide within one hour, peak drug levels at about two to three hours, and low but detectable levels at twenty-four hours.

Bioavailability studies have demonstrated that micronized glyburide tablets 3 mg provide serum glyburide concentrations that are not bioequivalent to those from nonmicronized glyburide tablets 5 mg. Therefore, the patient should be retitrated.

It has been reported that in a single-dose bioavailability study (see Figure A) in which subjects received micronized glyburide tablets 3 mg and nonmicronized glyburide tablets 5 mg with breakfast, the peak of the mean serum glyburide concentration-time curve was 97.2 ng/mL for the micronized glyburide tablets 3 mg and 87.5 ng/mL for nonmicronized glyburide tablets 5 mg. The mean of the individual maximum serum concentration values of glyburide (C_{max}) from micronized glyburide tablets 3 mg was 106 ng/mL and that from nonmicronized glyburide tablets 5 mg was 104 ng/mL. The mean glyburide area under the serum concentration-time curve (AUC) for this study was 568 ng x hr/mL for micronized glyburide tablets 3 mg and 746 ng x hr/mL for nonmicronized glyburide tablets 5 mg.

Figure A



——— Glyburide tablets (micronized)
- - - - - Glyburide tablets (nonmicronized)

Mean serum levels of glyburide, as reflected by areas under the serum concentration-time curve, increase in proportion to corresponding increases in dose. Multiple dose studies with glyburide in diabetic patients demonstrate drug level concentration-time curves similar to single dose studies, indicating no buildup of drug in tissue depots.

In a steady-state study in diabetic patients receiving micronized glyburide tablets 6 mg once daily or micronized glyburide tablets 3 mg twice daily, no difference was seen between the two dosage regimens in average 24 hour glyburide concentrations following two weeks of dosing. The once-daily and twice-daily regimens provided equivalent glucose control as measured by fasting plasma glucose levels, 4 hour postprandial glucose AUC values, and 24 hour glucose AUC values. Insulin AUC response over the 24 hour period was not different for the two regimens. There were differences in insulin response between the regimens for the breakfast and supper 4 hour postprandial periods, but these did not translate into differences in glucose control.

The serum concentration of glyburide in normal subjects decreased with a half-life of about four hours.

In single dose studies in fasting normal subjects who were administered glyburide tablets (micronized) in doses ranging from 1.25 mg to 5 mg, the degree and duration of blood glucose lowering is proportional to the dose administered and to the area under the drug level concentration-time curve. The blood glucose lowering effect persists for 24 hours following single morning doses in nonfasting diabetic patients. Under conditions of repeated administration in diabetic patients, however, there is no reliable correlation between blood drug levels and fasting blood glucose levels. A one year study of diabetic patients treated with glyburide showed no reliable correlation between administered dose and serum drug level.

The major metabolite of glyburide is the 4-trans-hydroxy derivative. A second metabolite, the 3-cis-hydroxy derivative, also occurs. These metabolites probably contribute no significant hypoglycemic action in humans since they are only weakly active (1/400th and 1/40th as active, respectively, as glyburide) in rabbits.

Glyburide is excreted as metabolites in the bile and urine, approximately 50% by each route. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine.

Sulfonylurea drugs are extensively bound to serum proteins. Displacement from protein binding sites by other drugs may lead to enhanced hypoglycemic action. *In vitro*, the protein binding exhibited by glyburide is predominantly non-ionic, whereas that of other sulfonylureas (chlorpropamide, tolbutamide, tolazamide) is predominantly ionic. Acidic drugs such as phenylbutazone, warfarin, and salicylates displace the ionic-binding sulfonylureas from serum proteins to a far greater extent than the non-ionic binding glyburide. It has not been shown that this difference in protein binding will result in fewer drug-drug interactions with glyburide in clinical use.

INDICATIONS AND USAGE

Glyburide tablets (micronized) are indicated as an adjunct to diet to lower the blood glucose in patients with non-insulin-dependent diabetes mellitus (Type II) whose hyperglycemia cannot be satisfactorily controlled by diet alone.

Glyburide may be used concomitantly with metformin when diet and glyburide or diet and metformin alone do not result in adequate glycemic control (see metformin insert).

In initiating treatment for non-insulin-dependent diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling the blood glucose and symptoms of hyperglycemia. The importance of regular physical activity should also be stressed, and cardiovascular risk factors should be identified and corrective measures taken where possible. If this treatment program fails to reduce symptoms and/or blood glucose, the use of an oral sulfonylurea or insulin should be considered. Use of glyburide must be viewed by both the physician and patient as a treatment in addition to diet and not as a substitution or as a convenient mechanism for avoiding dietary restraint. Furthermore, loss of blood glucose control on diet alone may be transient, thus requiring only short-term administration of glyburide.

During maintenance programs, glyburide should be discontinued if satisfactory lowering of blood glucose is no longer achieved. Judgment should be based on regular clinical and laboratory evaluations.

In considering the use of glyburide in asymptomatic patients, it should be recognized that controlling blood glucose in non-insulin-dependent diabetes has not been definitely established to be effective in preventing the long-term cardiovascular or neural complications of diabetes.

CONTRAINDICATIONS

Glyburide is contraindicated in patients with:

1. Known hypersensitivity or allergy to the drug.
2. Diabetic ketoacidosis, with or without coma. This condition should be treated with insulin.
3. Type I diabetes mellitus, as sole therapy.

SPECIAL WARNING ON INCREASED RISK OF CARDIOVASCULAR MORTALITY

The administration of oral hypoglycemic drugs has been reported to be associated with increased cardiovascular mortality as compared to treatment with diet alone or diet plus insulin. This warning is based on the study conducted by the University Group Diabetes Program (UGDP), a long-term prospective clinical trial designed to evaluate the effectiveness of glucose-lowering drugs

lation between administered dose and serum drug level.

The major metabolite of glyburide is the 4-trans-hydroxy derivative. A second metabolite, the 3-cis-hydroxy derivative, also occurs. These metabolites probably contribute no significant hypoglycemic action in humans since they are only weakly active (1/400th and 1/40th as active, respectively, as glyburide) in rabbits.

Glyburide is excreted as metabolites in the bile and urine, approximately 50% by each route. This dual excretory pathway is qualitatively different from that of other sulfonylureas, which are excreted primarily in the urine.

Sulfonylurea drugs are extensively bound to serum proteins. Displacement from protein binding sites by other drugs may lead to enhanced hypoglycemic action. *In vitro*, the protein binding exhibited by glyburide is predominantly non-ionic, whereas that of other sulfonylureas (chlorpropamide, tolbutamide, tolazamide) is predominantly ionic. Acidic drugs such as phenylbutazone, warfarin, and salicylates displace the ionic-binding sulfonylureas from serum proteins to a far greater extent that the non-ionic binding glyburide. It has not been shown that this difference in protein binding will result in fewer drug-drug interactions with glyburide in clinical use.

INDICATIONS AND USAGE

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UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide (1.5 grams per day) had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. A significant increase in total mortality was not observed, but the use of tolbutamide was discontinued based on the increase in cardiovascular mortality, thus limiting the opportunity for the study to show an increase in overall mortality. Despite controversy regarding the interpretation of these results, the findings of the UGDP study provide an adequate basis for this warning. The patient should be informed of the potential risks and advantages of glyburide tablets and of alternative modes of therapy.

Although only one drug in the sulfonylurea class (tolbutamide) was included in this study, it is prudent from a safety standpoint to consider that this warning may also apply to other oral hypoglycemic drugs in this class, in view of their close similarities in mode of action and chemical structure.

PRECAUTIONS

Bioavailability studies have demonstrated that micronized glyburide tablets 3 mg provide serum glyburide concentrations that are not bioequivalent to those from nonmicronized glyburide tablets 5 mg. Therefore, patients should be retitrated when transferred from nonmicronized glyburide tablets or other oral hypoglycemic agents.

General

Hypoglycemia: All sulfonylureas are capable of producing severe hypoglycemia. Proper patient selection and dosage and instructions are important to avoid hypoglycemic episodes. Renal or hepatic insufficiency may cause elevated drug levels of glyburide and the latter may also diminish gluconeogenic capacity, both of which increase the risk of serious hypoglycemic reactions. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency, are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. Hypoglycemia may be difficult to recognize in the elderly and in people who are taking beta-adrenergic blocking drugs. Hypoglycemia is more likely to occur when caloric intake is deficient, after severe or prolonged exercise, when alcohol is ingested, or when more than one glucose lowering drug is used. The risk of hypoglycemia may be increased with combination therapy.

Loss of Control of Blood Glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection or surgery, a loss of control may occur. At such times it may be necessary to discontinue glyburide tablets and administer insulin.

The effectiveness of any hypoglycemic drug, including glyburide, in lowering blood glucose to a desired level decreases in many patients over a period of time which may be due to progression of the severity of diabetes or to diminished responsiveness to the drug. This phenomenon is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective in an individual patient when glyburide is first given. Adequate adjustment of dose and adherence to diet should be assessed before classifying a patient as a secondary failure.

Information for Patients: Patients should be informed of the potential risks and advantages of glyburide tablets and of alternative modes of therapy. They also should be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of urine and/or blood glucose.

The risk of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members. Primary and secondary failure also should be explained.

Laboratory Tests

Therapeutic response to micronized glyburide tablets should be

monitored by frequent urine glucose tests and periodic blood glucose tests. Measurements of glycosylated hemoglobin levels may be helpful in some patients.

Drug Interactions

The hypoglycemic action of sulfonylureas may be potentiated by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents. When such drugs are administered to a patient receiving glyburide, the patient should be observed closely for hypoglycemia. When such drugs are withdrawn from a patient receiving glyburide, the patient should be observed closely for loss of control.

Certain drugs tend to produce hyperglycemia and may lead to loss of control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving glyburide, the patient should be closely observed for loss of control. When such drugs are withdrawn from a patient receiving glyburide, the patient should be observed closely for hypoglycemia.

A possible interaction between glyburide and ciprofloxacin, a fluoroquinolone antibiotic, has been reported, resulting in a potentiation of the hypoglycemic action of glyburide. The mechanism of action for this interaction is not known.

A potential interaction between oral miconazole and oral hypoglycemic agents leading to severe hypoglycemia has been reported. Whether this interaction also occurs with the intravenous, topical or vaginal preparations of miconazole is not known.

Metformin: In a single-dose interaction study in NIDDM subjects, decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain. Coadministration of glyburide and metformin did not result in any changes in either metformin pharmacokinetics or pharmacodynamics.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in rats at doses up to 300 mg/kg/day for 18 months showed no carcinogenic effects. Glyburide is nonmutagenic when studied in the Salmonella microsome test (Ames test) and in the DNA damage/alkaline elution assay.

No drug-related effects were noted in any of the criteria evaluated in the two-year oncogenicity study of glyburide in mice.

Pregnancy

Teratogenic Effects: Pregnancy Category B

Reproduction studies have been performed in rats at doses up to 500 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to glyburide. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Because recent information suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities, many experts recommend that insulin be used during pregnancy to maintain blood glucose as close to normal as possible.

Nonteratogenic Effects: Prolonged severe hypoglycemia (4 to 10 days) has been reported in neonates born to mothers who were receiving a sulfonylurea drug at the time of delivery. This has been reported more frequently with the use of agents with prolonged half-lives. If glyburide tablets are used during pregnancy, it should be discontinued at least two weeks before the expected delivery date.

Nursing Mothers

Although it is not known whether glyburide is excreted in human milk, some sulfonylurea drugs are known to be excreted in human milk. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If the drug is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Hypoglycemia: See **PRECAUTIONS** and **OVERDOSAGE** Sections.

Gastrointestinal Reactions: Cholestatic jaundice and hepatitis may occur rarely; glyburide tablets should be discontinued if this occurs. Liver function abnormalities, including isolated transaminase elevations, have been reported.

Gastrointestinal disturbances, *e.g.*, nausea, epigastric fullness, and heartburn are the most common reactions, having occurred in 1.8% of treated patients during clinical trials. They tend to be dose related and may disappear when dosage is reduced.

Dermatologic Reactions: Allergic skin reactions, *e.g.*, pruritus, erythema, urticaria, and morbilliform or maculopapular eruptions occurred in 1.5% of treated patients during clinical trials. These may be transient and may disappear despite continued use of glyburide. If skin reactions persist, the drug should be discontinued.

Porphyria cutanea tarda and photosensitivity reactions have been reported with sulfonylureas.

Hematologic Reactions: Leukopenia, agranulocytosis, thrombocytopenia, hemolytic anemia, aplastic anemia, and pancytopenia have been reported with sulfonylureas.

Metabolic Reactions: Hepatic porphyria and disulfiram-like reactions have been reported with sulfonylureas; however, hepatic porphyria has not been reported with glyburide and disulfiram-like reactions have been reported very rarely.

Cases of hyponatremia have been reported with glyburide and all other sulfonylureas, most often in patients who are on other medications or have medical conditions known to cause hyponatremia or increase release of antidiuretic hormone. The syndrome of inappropriate antidiuretic hormone (SIADH) secretion has been reported with certain other sulfonylureas, and it has been suggested that these sulfonylureas may augment the peripheral (antidiuretic) action of ADH and/or increase release of ADH.

Other Reactions: Changes in accommodation and/or blurred vision have been reported with glyburide and other sulfonylureas. These are thought to be related to fluctuation in glucose levels.

In addition to dermatologic reactions, allergic reactions such as angioedema, arthralgia, myalgia and vasculitis have been reported.

OVERDOSAGE

Overdosage of sulfonylureas, including glyburide, can produce hypoglycemia. Mild hypoglycemic symptoms, without loss of consciousness or neurological findings, should be treated aggressively with oral glucose and adjustments in drug dosage and/or meal patterns. Close monitoring should continue until the physician is assured that the patient is out of danger. Severe hypoglycemic reactions with coma, seizure, or other neurological impairment occur infrequently, but constitute medical emergencies requiring immediate hospitalization. If hypoglycemic coma is diagnosed or

reported with sulfonylureas.

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DOSAGE AND ADMINISTRATION

Patients should be retitrated when transferred from nonmicronized glyburide tablets or other oral hypoglycemic agents.

There is no fixed dosage regimen for the management of diabetes mellitus with glyburide tablets (micronized) or any other hypoglycemic agent. In addition to the usual monitoring of urinary glucose, the patient's blood glucose must also be monitored periodically to determine the minimum effective dose for the patient; to detect primary failure, *i.e.*, inadequate lowering of blood glucose at the maximum recommended dose of medication; and to detect secondary failure, *i.e.*, loss of adequate blood glucose lowering response after an initial period of effectiveness. Glycosylated hemoglobin levels may also be of value in monitoring the patient's response to therapy.

Short-term administration of glyburide may be sufficient during periods of transient loss of control in patients usually controlled well on diet.

Usual Starting Dose

The suggested starting dose of glyburide tablets (micronized) is 1.5 to 3 mg daily, administered with breakfast or the first main meal. Those patients who may be more sensitive to hypoglycemic drugs should be started at 0.75 mg daily. (See **PRECAUTIONS** Section for patients at increased risk.) Failure to follow an appropriate dosage regimen may precipitate hypoglycemia. Patients who do not adhere to their prescribed dietary and drug regimen are more prone to exhibit unsatisfactory response to therapy.

Transfer From Other Hypoglycemic Therapy: Patients Receiving Other Oral Antidiabetic Therapy: Patients should be retitrated when transferred from nonmicronized glyburide tablets or other oral hypoglycemic agents. The initial daily dose should be 1.5 to 3 mg. When transferring patients from oral hypoglycemic agents other than chlorpropamide to micronized glyburide tablets, no transition period and no initial or priming dose are necessary. When transferring patients from chlorpropamide, particular care should be exercised during the first two weeks because the prolonged retention of chlorpropamide in the body and subsequent overlapping drug effects may provoke hypoglycemia.

Patients Receiving Insulin: Some Type II diabetic patients being treated with insulin may respond satisfactorily to micronized glyburide. If the insulin dose is less than 20 units daily, substitution of glyburide tablets (micronized) 1.5 to 3 mg as a single daily dose may be tried. If the insulin dose is between 20 and 40 units daily, the patient may be placed directly on glyburide tablets (micronized) 3 mg daily as a single dose. If the insulin dose is more than 40 units daily, a transition period is required for conversion to micronized glyburide tablets. In these patients, insulin dosage is decreased by 50% and glyburide tablets (micronized) 3 mg daily is started. Please refer to **Titration to Maintenance Dose** for further explanation.

Titration to Maintenance Dose

The usual maintenance dose is in the range of 0.75 to 12 mg daily, which may be given as a single dose or in divided doses (See **Dosage Interval** Section). Dosage increases should be made in increments of no more than 1.5 mg at weekly intervals based upon the patient's blood glucose response.

No exact dosage relationship exists between micronized glyburide and the other oral hypoglycemic agents including nonmicronized glyburide tablets. Although patients may be transferred from the maximum dose of other sulfonylureas, the maximum starting dose of 3 mg of glyburide tablets (micronized) should be observed. A maintenance dose of 3 mg of glyburide tablets (micronized) provides approximately the same degree of blood glucose control as 250 to 375 mg chlorpropamide, 250 to 375 mg tolazamide, 5 mg of nonmicronized glyburide tablets, 500 to 750 mg acetohexamide, or 1000 to 1500 mg tolbutamide.

When transferring patients receiving more than 40 units of insulin daily, they may be started on a daily dose of glyburide tablets (micronized) 3 mg concomitantly with a 50% reduction in insulin dose. Progressive withdrawal of insulin and increase of glyburide tablets (micronized) in increments of 0.75 to 1.5 mg every 2 to 10 days is then carried out. During this conversion period when both insulin and glyburide tablets are being used, hypoglycemia may rarely occur. During insulin withdrawal, patients should test their urine for glucose and acetone at least three times daily and report results to their physician. The appearance of persistent acetonuria with glycosuria indicates that the patient is a Type I diabetic who requires insulin therapy.

Concomitant Glyburide and Metformin Therapy: Glyburide tablets (micronized) should be added gradually to the dosing regimen of patients who have not responded to the maximum dose of metformin monotherapy after four weeks (see Usual Starting Dose and Titration to Maintenance Dose). Refer to metformin package insert.

With concomitant glyburide and metformin therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the optimal dose of each drug needed to achieve this goal. With concomitant glyburide and metformin therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken (see **PRECAUTIONS** section).

Maximum Dose

Daily doses of more than 12 mg are not recommended.

Dosage Interval

Once-a-day therapy is usually satisfactory. Some patients, particularly those receiving more than 6 mg daily, may have a more satisfactory response with twice-a-day dosage.

Specific Patient Populations

Glyburide tablets are not recommended for use in pregnancy or for use in pediatric patients.

In elderly patients, debilitated or malnourished patients, and patients with impaired renal or hepatic function, the initial and maintenance dosing should be conservative to avoid hypoglycemic reactions. (See **PRECAUTIONS** Section.)

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with glycosuria [illegible]
requires insulin therapy.

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HOW SUPPLIED

Glyburide Tablets 1.5 mg- is a white oval tablet, bisected on one side, debossed with "MO3" and "1.5", and with "MOVA" on the other side - bottles of 100, 500 and 1000 tablets.

Glyburide Tablets 3 mg- is a blue oval shape tablet, bisected on one side, debossed with "MO4" and "3.0", and with "MOVA" on the other side - bottles of 100, 500 and 1000 tablets.

Glyburide Tablets 4.5 mg- is an oval light green tablet, bisected on one side, debossed with "MO6" and "4.5", and with "MOVA" on the other side - bottles of 100 and 1000 tablets.

Glyburide Tablets 6 mg- is a light yellow oval tablet, bisected on one side, debossed with "MO7" and "6.0", and with "MOVA" on the other side - bottles of 100, 500 and 1000 tablets.

1.5 mg	Bottles of 100	NDC 55370-146-07
	Bottles of 500	NDC 55370-146-08
	Bottles of 1000	NDC 55370-146-09
3 mg	Bottles of 100	NDC 55370-147-07
	Bottles of 500	NDC 55370-147-08
	Bottles of 1000	NDC 55370-147-09
4.5 mg	Bottles of 100	NDC 55370-149-07
	Bottles of 1000	NDC 55370-149-09
6 mg	Bottles of 100	NDC 55370-506-07
	Bottles of 500	NDC 55370-506-08
	Bottles of 1000	NDC 55370-506-09

The tablet can be easily divided in half for a more flexible dosing regimen. Press gently on the score and the tablet will split in even halves.

CAUTION: Federal law prohibits dispensing without prescription.

Store at controlled room temperature 15° to 30° C (59° to 86° F). Dispensed in well closed containers with safety closures. Keep container tightly closed.

Mantactured by
MOVA PHARMACEUTICAL CORPORATION
Caguas, Puerto Rico 00725,USA
Item 632301MV Revised 06/97

MOVA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074591

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO.5

2. ANDA # 74-591

3. NAME AND ADDRESS OF APPLICANT

MOVA Pharmaceutical Corporation
Attention: Claribel Velez
Calle A (Zafiro) Carr. 1 Km. 34.18 Urb. Industrial
Villa Blanca, Caguas, PR 00725

4. LEGAL BASIS FOR SUBMISSION

Attachment 1 contained a letter, dated February 17, 1995 to OGD, which informed UpJohn on 2/8/95, that patent # 4,916,163 for Glyburide Tablets and patent # 4,735,805 for bisectable tablets, will not be infringed by Mova's manufacture, use or sale of Glyburide Tablets.

A copy of UpJohn's returned receipt form for the letter was attached.

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME

Glyburide Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR:

N/A

9. AMENDMENTS AND OTHER DATES:

Firm:

12/09/94	ANDA submission (received on 12/16/94) See Addendum #2 to Chemistry review #4 for a list of the firms amendments and other correspondences.
08/26/97	Amendment (Re: Labeling)
10/24/97	Amendment (Re: Labeling FPL for 500s)
10/31/97*	Minor Amendment in response to TA letter(Re:- Changes in CMC for drug substance & excipients & drug product per USP changes. Inf for 500s C/C system & Labeling Updates.)
11/06/97*	Unsolicited Amendment (Re: Additional C/C info).
12/10/97*	Telephone Amendment (Hard copy to follow).

* Amendments subject to this review.

FDA:

02/11/97	Tentative Approval letter.
10/30/97	Approval Summary - Labeling
12/9/97	Record of Telephone Conversation

10. PHARMACOLOGICAL CATEGORY

See review #1.

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)

See review #4.

13. DOSAGE FORM

Tablets/oral

14. POTENCY

1.5 mg, 3 mg, 4.5 mg, 6 mg

15. CHEMICAL NAME AND STRUCTURE

See review #1.

16. RECORDS AND REPORTS

N/A

17. COMMENTS

Three minor chemistry deficiencies were found in the 10/31/97 amendment.

No deficiencies found in the 11/6/97 amendment.

The three minor deficiencies found in the 10/31/97 amendment were corrected in Mova's telephone amendment of 12/10/97.

Labeling found acceptable on 10/31/97. Labeling requires minor revisions post-approval.

Bio found acceptable on 9/12/95.

EER found acceptable on 4/2/96. However since it is more than 1 year old, an updated EER should be sent to compliance ASAP.

Methods were satisfactorily validated by San Juan District Lab on 1/9/97. Mova has acknowledged that the USP method is official, but will use their own method since it was shown to be stability indicating and validated successfully by SJN-DO.

Glyburide Tablets became official after the tentative approval letter was issued on 2/11/97. The drug product became official in the USP 23, Supplement #6 on 5/15/97. The drug substance was official in USP XXII.

18. CONCLUSIONS AND RECOMMENDATIONS

Application is approvable.

19. REVIEWER: DATE COMPLETED:

Stephen Sherken 12/11/97

cc: ANDA74-591
Division Copy
Field Copy

Endorsements:
HFD-625/S.Sherken/12-11-97
HFD-625/M.Smela/12-11-97
X:\NEW\FIRMSAM\MOVA\LTRS&REV\74591.RV5
F/T by: bc/12-15-97

12/16/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074591

BIOEQUIVALENCE REVIEW(S)

SEP 12 1995

Glyburide, 1.5 mg, 3 mg
4.5 mg and 6 mg Tablets
ANDA # 74-591
Reviewer: Man M. Kochhar

Mova Pharm Corp.
Caguas, Puerto Rico
Submission Date:
December 9, 1994

Review of Bioequivalence Study, Dissolution and Waivers Request

(Fasting and Non-fasting)

OBJECTIVE:

The objective of this study was to determine the bioequivalence of the 6.0 mg generic Glyburide tablet with the marketed 6 mg Glynase PresTab tablet in healthy subjects under fasting and non-fasting conditions. The effects of the food on the pharmacokinetics of glyburide were also evaluated.

INTRODUCTION:

Glyburide chemically belong to the class of sulfonylurea. It is a white crystalline compound and is sparingly soluble in water. There is no fixed dosage regimen for the management of diabetes mellitus with glyburide. The usual starting dose is 1.5 to 3.0 mg daily, administered with breakfast or the first main meal.

Glyburide appears to lower the blood glucose by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets. In addition to its blood glucose lowering action, glyburide produces a mild diuresis by enhancement of renal free water clearance.

Single dose studies with glyburide in normal subjects demonstrate absorption of glyburide within one hour, peak drug levels at about 2 to 3 hours, and low but detectable levels at 24 hours. Mean serum levels of glyburide, as reflected by area under the serum concentration-time curve, increase in proportion to corresponding increases in dose. The half-life was observed to be about 4 hours.

IN-VIVO STUDY:

The objective of this study was to compare the bioavailability of Mova Pharm and Upjohn (Glynase PresTab) 6.0 mg tablets under fasting and non-fasting conditions.

The bioequivalence study was conducted by

STUDY DESIGN:

1. The fasting study was designed as a randomized, single dose (6 mg tablet), two-way crossover bioequivalence study in 36 healthy volunteers (protocol # 940131).

2. The non-fasting study was designed as a randomized, three-way crossover, single dose (6 mg tablet) bioequivalence study in 18 healthy volunteers (protocol # 940132).

Subjects:

The study employed thirty-six (36) subjects for fasting study and eighteen (18) subjects for non-fasting study between the ages of 18-45, whose weight did not deviate by more than ±15% of the ideal for their height and age (Metropolitan Life Insurance Company Bulletin,1983). Volunteers without history of serious gastrointestinal, hepatic, cardiovascular, hematological or renal disease were employed. In addition, subjects were required to be without history of alcohol or drug use and prior sensitivity to drug product being tested.

Good health was ascertained from medical history, physical examination and routine laboratory tests (blood chemistry, hematology, urinalysis). The subjects were required not to take any prescription medications and/or OTC preparations for at least 7 days prior to the start and until the end of the study. The volunteers were not allowed to drink alcoholic beverages or caffeine-containing products for 24 hours prior to dosing until after completion of the study. Each subject signed a written informed consent.

The subjects remained in the clinic from 12 hours before dosing until after the 36-hour blood draw.

Methods:

The product and dosage employed in this study were as follows:

FASTING:

Treatment A. Test: One 6 mg glyburide tablet, lot # MKT0911 with 240 mL of 20% dextrose solution in water (Fasting).

Batch size: tablets, Expiry Date: n/a
Content Uniformity: 101.2% Date Manufactured: 3-26-94
Potency: 100.5%

Treatment B. Reference: One 6 mg Glynase PreTab tablet (Upjohn), lot # 417 XF with 240 mL of 20% dextrose solution in water (Fasting).

Expiry Date: 4/96. Content Uniformity: 101.7%
Potency: 101.4%

NON-FASTING:

Treatment C. Test: One 6 mg glyburide tablet, lot # MKT0911 with 240 mL of 20% dextrose solution in water (fasting).

Treatment D. Test: One 6 mg glyburide tablet, lot # MKT0911 with 240 mL of 20% dextrose solution in water (Non-fasting).

Treatment E. Reference: One 6 mg Glynase PresTab tablet (Upjohn), lot # 417 XF with 240 mL of 20% dextrose solution in water (Non-fasting).

In treatments # A, B and C subjects fasted for 10 hours prior to and 4 hours after the drug administration. Water ad lib was allowed except within 1 hours of drug administration.

In a non-fasting treatments # D and E subjects fasted overnight until 30 minutes prior to their schedule dosing times, when they were given a standard breakfast.

Ten (10) mL of venous blood were drawn into a Vacutainers with EDTA at 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 12, 16, 24, and 36 hours. The plasma was separated and promptly frozen for analysis.

At the time of dosing, each subject received 240 mL of 20% dextrose solution in water. Also, 60 mL of 20% dextrose solution in water was administered at following times after dosing: 0.25, 0.5, 0.75, 1.0, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75 and 4 hours.

Blood glucose determinations were performed before dosing and approximately 1, 2, 4, and 6 hours after dosing (determinations were performed within 19 minutes after the blood draws at these times).

WASHOUT PERIOD: 1 week

ANALYTICAL METHODOLOGY: Glyburide in plasma was measured by a

ASSAY VALIDATION:

DATA ANALYSIS:

Statistical significance of differences due to treatments, study days, dosing sequence, subjects within sequence, in plasma glyburide concentrations at each sampling time and its pharmacokinetic parameters were determined by analysis of variance (ANOVA) using Statistical Analysis Systems (SAS) general linear model (GLM) procedure. 90% confidence intervals (two one-sided t-test) were calculated for glyburide pharmacokinetic parameters.

IN VIVO BIOEQUIVALENCE STUDY RESULTS:

FASTING STUDY

Treatment A & B

All thirty-six (36) subjects completed the crossover. The plasma samples from the 36 subjects were assayed for glyburide as per the protocol. The results of the study comparing the bioavailability of glyburide (test) and Glynase PresTab (reference) products are given in Table 1 and 2. The mean plasma glyburide concentrations for test and reference treatments are given in Figure 1.

TABLE 1

Mean Plasma Concentration of Glyburide (N= 36)

Time (hours)	Mova's Glyburide Lot # MKT0911 ng/mL (%CV)	Upjohn's Glynase PresTab Lot # 417XF ng/mL (%CV)	T/R
0.00	0.0	0.0	
0.5	16.40 (167)	6.66 (127)	2.46
1	48.84 (101)	25.22 (118)	1.94
1.5	75.43 (94)	38.24 (137)	1.97
2.0	80.84 (94)	52.28 (114)	1.55
2.5	84.40 (86)	66.57 (101)	1.27
3.0	88.68 (82)	83.87 (86)	1.06
4.0	85.51 (93)	84.59 (81)	1.01
5.0	79.76 (64)	86.65 (61)	0.92
6.0	97.89 (72)	122.66 (51)	0.79
8.0	88.35 (76)	96.84 (62)	0.91
10.0	74.11 (73)	65.39 (58)	1.13
12.0	46.78 (81)	40.09 (70)	1.17
16.0	17.34 (103)	16.40 (75)	1.06
24.0	3.42 (151)	5.80 (141)	0.59
30.0	0.84 (307)	2.00 (219)	0.42
36.0	0.38 (419)	0.68 (486)	0.56

TABLE 2

A Summary of Pharmacokinetic Parameters for 36 Subjects (%CV)

Parameters	Mova's Mean (CV%)	Upjohn's Mean (CV%)	T/R	90% Confidence Interval
AUC_{0-36} ng.hr/mL	1093.1 (34)	1078.3 (31)	1.01	97; 106
AUC_{inf} ng.hr/mL	1144.7 (34)	1141.6 (33)	1.00	95; 104

C_{max} ng/mL	192.2 (34)	181.9 (25)	1.06	95; 116
T_{max} hours	5.1 (55)	5.2 (37)	0.98	
K_{el} 1/hr	0.253 (46)	0.236 (50)	1.07	
$t_{1/2}$ hours	3.35 (48)	3.81 (56)	0.88	
Ln AUC_{0-36} ng.hr/mL	6.94 (2)	6.93 (2)	1.00	97; 106
Ln AUC_{inf} ng.hr/mL	6.99 (1)	6.99 (2)	1.00	96; 104
Ln C_{max} ng/mL	5.21 (5)	5.17 (4)	1.00	94; 115

The glyburide AUC_{0-36} and AUC_{inf} produced by Mova's formulation are 1.37% and 0.27% higher than the respective values for the reference drug. The C_{max} is 5.66% higher than the reference. The K_{el} and $t_{1/2}$ values differ by 7.2% and 12.07% respectively. The Tmax was 1.92% lower for the test drug. The firm did calculate Ln AUC and Ln Cmax for glyburide and the 90% confidence intervals for log-transformed parameters were 97 to 106 for Ln AUCo-t, 96 to 104 for Ln AUCinf and 94 to 115 for Ln Cmax.

The 90% confidence intervals for untransformed glyburide AUCo-t, AUCinf and C_{max} were well within 80 to 120 in a fasting study.

The glyburide concentration/time profiles of the two products showed significant differences at 0.5, 1.0. 1.5, 2.0, 6.0, 24, 30 and 36 hours after dosing.

No serious adverse effects were experienced by any subject during the study.

NON-FASTING

Treatment # C, D & E

Among the 18 subjects enrolled in the study, one subject did not complete the crossover. Subject # 6 was withdrawn from the study prior to period 2 dosing as he did not finished his entire breakfast. The study was completed with no major protocol violations. The results of the study comparing the bioavailability of glyburide under test fasting and test and reference non-fasting glyburide are given in Tables 3 and 4. The mean plasma glyburide concentrations are given in Figure 2.

TABLE 3

Mean Plasma Concentration of Glyburide (N=17)

Time Hours	Mova's Glyburide 6 mg Tablet ng/mL (CV%)	Upjohn's Glynase PresTab 6 mg Tablet ng/mL (CV%)	T/R (E/F)
	FASTING Treat. D	NON-FASTING Treat. E	NON-FASTING Treat. F	
0.0	0.00 (---)	0.00 (---)	0.00 (---)	0.00
0.5	21.38 (171)	9.88 (176)	4.42 (230)	2.23
1.0	58.86 (92)	50.99 (118)	42.78 (148)	1.19
1.5	80.28 (79)	102.52 (83)	84.15 (95)	1.22
2.0	97.53 (75)	163.73 (59)	127.13 (69)	1.29
2.5	94.79 (63)	175.45 (41)	140.82 (58)	1.25
3.0	110.51 (65)	174.23 (33)	143.85 (44)	1.21
4.0	102.07 (82)	148.25 (33)	129.93 (35)	1.14
5.0	97.57 (60)	119.19 (40)	120.05 (50)	0.99
6.0	106.36 (53)	115.28 (60)	119.80 (58)	0.96
8.0	68.60 (44)	68.96 (66)	97.21 (68)	0.71
10.0	43.20 (48)	40.84 (58)	55.30 (73)	0.74
12.0	28.50 (65)	23.07 (65)	26.72 (79)	0.87
16.0	12.44 (74)	7.54 (82)	7.75 (93)	0.97
24.0	8.47 (113)	1.52 (213)	0.76 (290)	2.00
30.0	3.12 (149)	1.24 (232)	0.00 (---)	0.00
36.0	1.34 (245)	0.47 (412)	0.00 (---)	0.00

TABLE 4

A SUMMARY OF PHARMACOKINETIC PARAMETERS FOR 17 SUBJECTS
Non-Fasting

Parameters	Mova's Glyburide Mean (CV%)	Upjohn's Glynase Prestab Mean (CV%)	T/R D/E
	Fasting Treatment C	Non-Fasting D	Non-Fasting E	
AUC_{0-36} ng.hr/mL	1058.7 (30)	1157.5 (30)	1143.6 (27)	1.01
AUC_{inf} ng.hr/mL	1206.5 (29)	1202.5 (29)	1174.5 (27)	1.02
C_{max} ng/mL	178.5 (31)	224.8 (22)	211.7 (25)	1.06
T_{max} hours	4.2 (42)	3.1 (48)	4.6 (50)	1.35

$t_{1/2}$ hours	5.46 (56)	3.87 (81)	2.43 (30)	1.59
K_{el} 1/hr	0.19 (75)	0.254 (44)	0.308 (29)	0.82
Ln AUC_{0-36} ng.hr/mL	6.9	7.0	7.0	
Ln AUC_{inf} ng.hr/mL	7.06	7.05	7.03	
Ln C_{max} ng/mL	5.14	5.39	5.32	

Fasted-Fed Comparison (Treatment C vs D) Mova:

Results for untransformed parameters showed increases of 9.33% and 25.94%, respectively, for AUC and Cmax after the administration of food. Mean Tmax after the fasted administration was 4.2 hours versus 3.1 hours after food administration.

Fed Comparison (Treatment D vs E) Mova vs Upjohn

The ratios for untransformed parameters were 1.01, 1.02, and 1.06 for AUCo-t, AUCinf and Cmax, respectively. Mean Tmax values were 3.1 and 4.6 for Mova (D) and Upjohn (E) products after food administration. The Kel and t1/2 values differ by 17.5% and 59.26%.

There were no serious adverse effects reported during the study.

On the basis of fasting and non-fasting in vivo bioavailability data it is determined that Mova's glyburide 6 mg tablets and Upjohn's Glynase PresTab 6 mg tablets are bioequivalent.

DISSOLUTION TEST RESULTS:

Two in vitro dissolution testing methods were used in this study. Method # 1 is required by the Division of Bioequivalence for glyburide tablets.

1. In vitro dissolution testing was conducted in 500 mL of 0.05 M Borate Buffer, pH 9.5 at 37°C using USP XXII apparatus 2 (Paddle) at 75 rpm. Results are presented in Table 5. Both the test and reference products meet the dissolution specifications of not less than of the labeled amount of the drug dissolved from the tablet in 30 minutes.

2. The dissolution testing was conducted in 900 mL of 0.1 M phosphate buffer, pH 7.4 at 37°C using USP XXII apparatus 2 (Paddle) at 50 rpm. Results are presented in Table 6. Both the test and reference products meet the dissolution specifications of not less than of the labeled amount of drug dissolved from the tablet in 45 minutes.

The batch size was ablets.

The lots of test and reference products employed in the in vitro dissolution test were identical to those employed in the in vivo bioequivalence study.

COMMENTS:

FASTING

Treatments A and B

1. The study was conducted in 36 healthy volunteers and samples from all subjects were assayed as per the protocol, comparing the plasma concentrations from Mova's glyburide, 6 mg tablet to that of reference (Glynase PresTab), 6 mg tablet manufactured by Upjohn.

The T/R ratios for glyburide AUC_{0-36}, AUC_{inf}, and C_{max} were within the range of 0.8 to 1.2.

2. The ratios of least-squares means for glyburide log- transformed parameters AUCo-t, AUCinf and Cmax were 101.2%, 99.7% and 103.9% respectively. Analysis of variance indicated no statistically significant treatment or sequence effects for AUC and C_{max}. The 90% confidence intervals are well within 80% to 125% for all the log-transformed pharmacokinetic parameters.

3. The assay validation studies conducted by the sponsor are acceptable to the Division of Bioequivalence

4. No serious side effects were observed.

5. The in vitro dissolution testing conducted on both the test and reference products show greater than of the labeled amount of glyburide dissolved in 30 minutes. The sponsor has conducted dissolution according to the specifications of the Division of Bioequivalence.

6. The in vivo fasting bioequivalence study and in vitro dissolution testing are acceptable.

NON-FASTING

Treatments C, D & E

1. Of the 18 subjects enrolled in the study, one subject did not complete the crossover. Subject # 6 was withdrawn from the study prior to Period 2 dosing as he did not complete his entire breakfast. The statistical analyses were performed on data from 17 subjects.

2. For Treatment D and E the ratios for AUCo-t, AUCinf, and Cmax of the test and reference formulations were 1.01, 1.02, and 1.06

respectively. The ratio for these parameters were well within the limits set by the Division of Bioequivalence. The ratios of least-squares means for the log-transformed parameters AUCo-t, AUCinf and Cmax were 97.4%, 95.4% and 111.5%, respectively.

ANOVA showed no statistically significant differences in products for any of the pharmacokinetic parameters.

3. The Mova and Upjohn glyburide 6 mg tablets, appear to show comparable bioavailability under non-fasting conditions. When these tablets were administered to non-fasting subjects, the mean values of the computed parameters were almost identical. Furthermore, administration of food with the Mova product produced little change in AUCinf, a marked increase in Cmax, and an earlier Tmax. Glynase PresTab and test glyburide tablets were shown to be bioequivalent in both fasting and non-fasting conditions.

4. No serious adverse events were recorded during this period.

DEFICIENCY: None

RECOMMENDATIONS:

1. The fasting and non-fasting bioequivalence studies conducted by Mova Pharmaceutical Corporation on its Glyburide 6 mg tablets, lot # MKT0911, comparing it to Glynase PresTab 6 mg tablets, lot # 417XF, manufactured by Upjohn has been found acceptable by the Division of Bioequivalence. The study demonstrate that under fasting and non-fasting conditions the Mova Pharmaceutical's Glyburide 6 mg tablets are bioequivalent to the reference product, Glynase PresTab 6 mg tablets, manufactured by Upjohn.

2. The formulation for 1.5 mg, 3.0 mg, 4.5 mg Glyburide tablets is proportionally similar to 6 mg Glyburide tablet which underwent an acceptable bioequivalent study under fasting and non-fasting conditions. The in vitro test results on 1.5 mg, 3.0 mg, 4.5 mg, and 6.0 mg are acceptable. The waiver of in vivo bioequivalence study requirement for Mova Pharmaceutical Corporation 1.5 mg, 3.0 mg and 4.5 mg tablets is granted. The 1.5 and 3.0 mg Glyburide tablets from Mova Pharmaceutical are, therefore, deemed bioequivalent to 1.5 mg and 3.0 mg Glynase PresTab tablets manufactured by Upjohn based on CFR 320.22 (d)(2).

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 500 mL of 0.05 M Borate Buffer, pH 9.5 at 37°C using USP XXIII apparatus 2 (paddle) at 75 rpm. The test should meet the following specifications:

> Not less than of the labeled amount of the drug in the tablet is dissolved in 45 minutes.

4. From the bioequivalence point of view, the firm has met the requirements for in vivo bioequivalence and in vitro dissolution

testing and the study is acceptable.

Man.M.Kochhar, Ph.D
Review Branch III
Division of Bioequivalence

RD INITIALLED RMHATRE
FT INITIALLED RMHATRE

Concur: _____ Date: 9/12/95
Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

MMKochhar/mmk/5-18-95: 7-28-95; 8-9-95; 74-591 BIO

cc: ANDA # 74-591 original, HFD-630, HFD-600 (Hare), HFD-344 (CViswanathan) HFD-658 (Mhatre, Kochhar), Drug File.

(Please select Typeover for Input.)

Table 6 . In Vitro Dissolution Testing

Drug (Generic Name): Glyburide
Dose Strength: 6 mg
ANDA No.: 74-591
Firm: Mova
Submission Date: December 9, 1994
File Name:

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: Volume: 900 0.1 M Phosphate Buffer, pH 7.4
Specifications: NLT in 45 minutes
Reference Drug: Glynase PresTab

Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Lot # MKT0911 Strength 6 MG			Reference Product Lot # 417XF Strength 6 MG		
	Mean %	Range	%RSD	Mean %	Range	%RSD
10	59		11.4	73		4.6
30	82		4.7	90		2.2
45	94		3.3	96		1.5
60	99		4.8	98		1.7

Sampling Times (Minutes)	Test Product Lot # MKT097V Strength(4.5 mg)			Reference Product Lot # Strength(mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
15	71		2.5			
30	88		1.3			

45	96		2.3			
60	98		1.3			

Sampling Times (Minutes)	Test Product Lot # MKT096V Strength(3.0 mg)			Reference Product Lot # 127 JP Strength(3.0 mg)		
	Mean %	Range	%RSD	Mean %	Range	%RSD
15	85		6.5	79		1.5
30	99		1.8	92		2.4
45	102		2.4	97		1.7
60	105		3.4	101		1.7

Sampling Times (Minutes)	Test Product Lot # MKT 095V Strength(1.5 mg)			Reference Product Lot # 011JM Strength(1.5 mg)		
	Mean %	Range	%CV	Mean %	Range	%RSD
15	56		17.3	83		18.2
30	95		4.3	92		15.3
45	103		3.5	95		9.1
60	105		2.7	98		7.9

TABLE 7

FORMULATIONS

	TABLETS			
INGREDIENTS	**6.0 mg**	**4.5 mg**	**3.0 mg**	**1.5 mg**
Glyburide Micronized	6.30*	4.725*	3.15*	1.575*
Lactose Monohydrate, NF				
Colloidal Silicon Dioxide, NF				
Pregelatinized Starch,NF				
Magnesium Stearate, NF				
FD&C Blue #1,				
FD&C Yellow # 10				
FD&C Yellow # 6				
TOTAL WEIGHT	**175.00**	**175.0**	**175.0**	**175.0**

*** Includes 5% excess**

Figure 1

Project No. 940131

Mean Human Plasma GLYBURIDE Concentrations

(Semi – Log Plot)

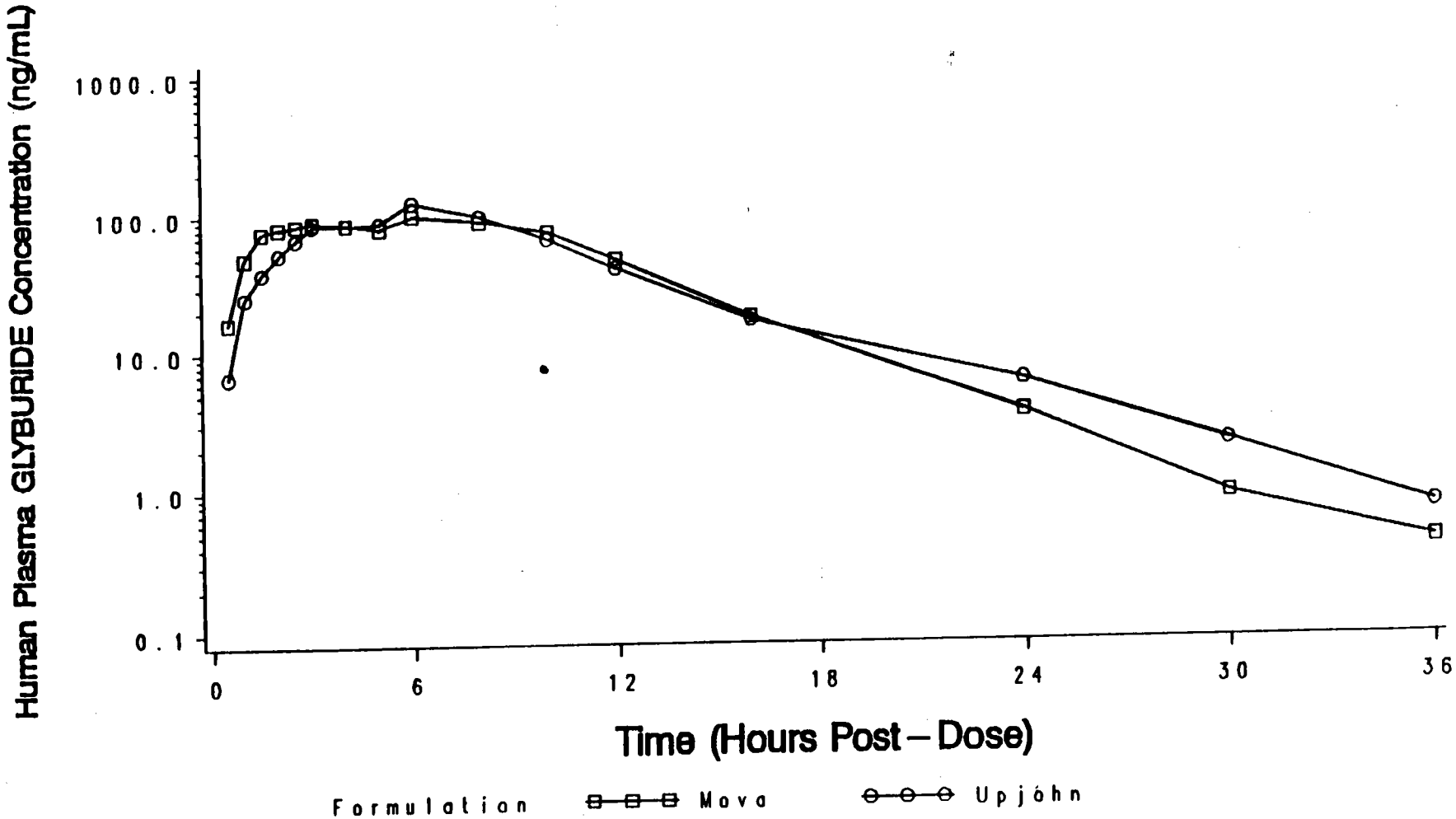

Figure 2

Project No. 940131

Mean Human Plasma GLYBURIDE Concentrations

(Linear Plot)